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Ranibizumab with transpupillary thermotherapy for clinical efficacy in wet age-related macular degeneration

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玻璃体腔注射 Ranibizumab 联合经瞳孔温热疗法治疗年龄相关性黄斑变性

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摘要

目的:观察玻璃体腔注射 Ranibizumab 联合经瞳孔温热疗法(TTT)治疗渗出型年龄相关性黄斑变性的临床疗效及安全性。

方法:选取来我院就诊并通过病史、临床症状及眼底血管照影(FFA/ICGA)和光学相干断层扫描(OCT)等辅助检查确诊的渗出型年龄相关性黄斑变性的患者 160 例(160 眼),随机分为联合组和对照组,联合组给予单次行玻璃体腔注射 Ranibizumab,7d 后行 TTT 治疗,对照组仅行 TTT 治疗,随访 1a,分别于治疗后 1wk;1,6mo;1a,观察患者的最佳矫正视力、散瞳后眼底的变化及眼底血管照影(FFA/ICGA)及 OCT 的检查。

结果:观察期末,联合组最佳矫正视力提高 34 例(42.50%),对照组最佳矫正视力提高 16 例(20.00%),差异具有统计学意义(P<0.05)。治疗后 1wk;1,6mo;1a 联合组和对照组的荧光渗透有效率分别为(88.75%,62.50%);(91.25%,65.00%);(86.25%,61.25%);(78.75%,51.25%)。治疗后 1wk;1,6mo;1a 联合组和对照组黄斑中心厚度分别为:(347.43±36.96)μm 和(423.58±29.03)μm;(287.78±34.16)μm 和(387.14±32.98)μm;(301.75±37.21)μm 和(415.40±31.38)μm;(326.17±27.39)μm 和(436.44±35.49)μm,两组相比,差异具有统计学意义(P<0.05)。

结论:玻璃体腔注射 Ranibizumab 联合经瞳孔温热疗法治疗渗出型年龄相关性黄斑变性,能够使患者的视力得到改善,病灶渗漏停止或减轻,促进黄斑区出血、水肿及渗出的吸收,安全、疗效可靠,是一种有效的临床治疗方法。

关键词:经瞳孔温热疗法;渗出型年龄相关性黄斑变性;Ranibizumab;玻璃体腔注射

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Abstract

• AIM: To observe the efficacy and safety of intravitreal injection of Ranibizumab with transpupillary thermotherapy (TTT) in patients with wet age-related macular degeneration (AMD).

• METHODS: Totally 160 wet age-related macular degeneration patients (160 eyes) were selected, which have been diagnosed through history, clinical symptoms and fundus angiography (FFA/ICGA) as well as optical coherence tomography (OCT) and other auxiliary examinations in our hospital. All these patients were randomly divided into the combined group and the control group. Combined group was given a single intravitreal injection Ranibizumab and applied the TTT treatment after seven days, while the control group only received the TTT treatment and was being monitored for 1y. The patients' best corrected visual acuity, fundus angiography (FFA/ICGA) and OCT examination were observed after 1wk, 1mo, 6mo and 1y of the treatment, respectively.

• RESULTS: By the end of the observation period, there were 34 cases (42.50%) out of the combined group whose the best corrected visual acuity have improved, while 16 cases from the control group (20.00%) whose best corrected visual acuity have improved. The difference between the two groups showed statistically significance (P<0.05). More specifically, the fluorescent penetrant rates are (88.75%, 62.50%), (91.25%, 65.00%), (86.25%, 61.25%), (78.75%, 51.25%), respectively, in both groups after 1wk, 1mo, 6mo and 1y treatment, and also the corresponding central macular thickness (CMT) were (347.43±36.96) μm and (423.58±29.03) μm, (287.78±34.16) μm and (387.14±32.98) μm, (301.75±37.21) μm and (415.40±31.38) μm, (326.17±27.39) μm and (436.44±35.49) μm. In a nutshell, the difference between the two groups were statistically significant (P<0.05).

• CONCLUSION: Intravitreal injection of Ranibizumab with TTT treatment applied among patients with wet age-related macular degeneration (AMD) could improve patients' vision, stop or reduce the leakage of the lesion, as well as promote the absorption of macular hemorrhage, edema and exudation, which could be considered as a safe, reliable and effective clinical treatment.

• KEYWORDS: transpupillary thermotherapy; wet age-related macular degeneration; Ranibizumab; intravitreal injection
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INTRODUCTION

Age-related macular degeneration (AMD) is one of the major age-related eye diseases which could cause blindness of people who are more than 50y old in Western countries[1]. In China, with the aging of the population in recent years, the incidence of AMD is increasing year by year, and getting more attention by domestic and foreign research scholars. AMD can be divided into dry and wet according to the clinical and pathological findings. The dry is mainly for macular retinal pigment epithelium atrophy and generally does not cause total blindness in patients, although the wet is only 10% of the AMD[2] which often leads to severe visual loss with the poor prognosis and recurrence rate since the fiber is always considered as retinal degeneration, choroidal neovascularization (CNV) and discoid scarring. Hence there is no effective method of treatment currently. Transpupillary thermotherapy (TTT) is a method that utilizes semiconductor laser, low intensity radiation, and heat transport through the pupil to the pigment epithelium and choroid. In this case, it will not cause coagulation of the local tissue of the blood vessel occlusion[3,4]. Currently, Ranibizumab is known as the strongest anti-vascular endothelial growth factor (VEGF) biologics; because it has a small molecular weight also can penetrate the retina and reduce the formation of new blood vessels in a better way. Therefore, we use intravitreal Ranibizumab with TTT treatment of wet AMD to study the efficacy of this approach and its clinical significance[5,6].

SUBJECTS AND METHODS

Subjects Our experiments should comply with the Declaration of Helsinki, approved with the ethics committee, and signed the informed consent. Totally 160 wet AMD patients (160 eyes) of the first affiliated hospital of Liaoning medical university in ophthalmology clinic were selected, from March 2012 to October 2013, among 88 male cases and 72 female cases, and the age was from 51 to 79 years old with an average of 66. 5 years old, as well as the duration was from 6mo to 3y with an average of 1. 6y. These patients were randomly divided into two groups: the combined group and the control group, 80 cases in each group (80 eyes). All enrolled patients met the following conditions: (1) Vision: conscious patients have varying degrees of vision loss, eyes shadow, central scotoma, visual distortion and decreased contrast sensitivity and *etc*. Best corrected visual acuity is between 0. 01-0. 4, and early treatment diabetic retionopathy study (ETDRS) number of letters is in 5-50mo; (2) IOP: in the normal range; (3) Slit lamp microscope: the anterior segment examination shows no abnormal; (4) After dilated fundus examination: eyes with varying degrees of macular edema, oozing and bleeding; (5) Fundus angiography (FFA/ICGA): lesions visible on the different levels of fluorescein leakage or bleeding is associated with a fluorescent pigment epithelium around the block and choroidalneovascularization (CNV) strong fluorescence serous detachment zone performance; (6) Optical coherence tomography (OCT): visible lesions unusually high reflective areas and macular edema, thickening, the central macular thickness (CMT) is at 279-602 (an average of 412. 68±74. 12) μm. All eyes are excluded from corneal disease, cataract, glaucoma, vitreous opacities and severe high blood pressure, diabetes, liver and kidney dysfunction and other factors observations, and without eye surgery, retinal laser photocoagulation and injection history of the ball in the past, and *etc*.

Methods

Intravitreal injection of Ranibizumab All patients for admission should take a parallel routine preoperative examination, be given a detailed account of the surgical purposes, risks, potential complications, and postoperative care, sign the informed consent of intravitreal Ranibizumab, apply eye drops 6 times a day in order to clean the conjunctival and prevent infection 2d before the injection application of tobramycin. Intravitreal injection of Ranibizumab is conducted in strict accordance with the formal steps in a sterile operating room. Before operating, we used the proparacaine drops to topical anesthesia on the temporal distance Angle sclera margin of 3. 5 to 4. 0 mm (the ciliary body flat) into the needle, and slowly injected 0. 5 mg/0. 05 mL Ranibizumab into the vitreous cavity, and then removed the needle after needle mouth swab pressed 2-3min. After referring to measuring intraocular pressure Tn, binding up with pad were performed. After seven days, the combined groupapplied the treatment of TTT[7-9].

The transpupillary thermotherapy treatment All patients are informed before passing through TTT for the purpose and possible risks and complications, and patients need sign the informed consent. Before conducting treatment on the affected eye with compound tropicamide eye drops sufficiently dilated, for surface anesthesia drops proparacaine, the patient´s head is fixed on the slit lamp, the oculer laser mirror is placed in a 90° in the affected eye, and with the wavelength of 810 nm joint near infrared laser light fiber in the lesion site. In the beginning, light control is between 60-120s, energy control is in 100-300 mW, spot diameter is between 1. 2-3. 0 mm, until a gray mild or no damage as a benchmark appears. With the change of the colors, the energy control should also be changed accordingly, due to the standardization of energy problem, reactions to TTT individual difference is big, this is all done by an experienced doctor whose treatment operation to ensure that all lesion site will have the corresponding change[10,11].

Table 1 The two groups in BCVA compare different time periods (Total efficiency %)

Group	Before therapy average BCVA	After therapy			
		One week	One month	Six months	One year
Combination group	0.30	86.25%	90.00%	88.75%	83.75%
Control group	0.25	73.75%	67.50%	63.75%	47.50%
P	0.81	0.009[a]	0.003[a]	0.006[a]	0.002[a]

[a]Statistically significant ($P<0.05$).

Table 2 The two groups in fluorescence leakage compare different time periods (Efficiency %)

Group	Before therapy average leakage	After therapy			
		One week	One month	Six months	One year
Combination group	2.0 PD	88.75%	91.25%	86.25%	78.75%
Control group	2.5 PD	62.50%	65.00%	61.25%	51.25%
P	0.79	0.004[a]	0.003[a]	0.005[a]	0.006[a]

[a]Statistically significant($P<0.05$).

Follow-up observations Observe the best corrected visual acuity and FFA/ICGA and optical coherence fault scanning imaging (OCT) after 1wk, 1mo, 6mo and 1y treatment, respectively. (1) Best corrected visual acuity: adopt international standards of eye examination for eye vision correction. Visual acuity improved: improved ≥2; Vision loss: decreased ≥2; Vision stable: fluctuations within a row; If the visual acuity is <0.1 then change 0.02 to 1 line. (2) FFA/ICGA: assess the treatment effect according to leakage. Stop leakage: FFA/ICGA check without leakage; Reduce leakage: FFA/ICGA check for leakage area reduced ≥50%; Increase leakage: FFA/ICGA check for leakage area expanded than before the treatment; Continue leakage: FFA/ICGA check for leakage area decreased ≤50%. (3) OCT: use Heidelberg SPECTRALIS frequency-domain OCT to measure the central macular thickness (CMT), and in order to ensure the accuracy of the experiment, all check of the patients should be operated by the same technician[12,13].

Statistical Analysis Statistical analysis is gained by using SPSS 10.0. The data is compared between the two groups by using the *t*-test, while the count data statistics is gained by using x^2 test. $P<0.05$ is considered to be statistically significant.

RESULTS

Best Corrected Visual Acuity After 1wk therapy: in combined group, the total effective rate is 86.25% (69/80), while in control group, the total effective rate is 73.75% (59/80); 1mo after therapy: in combined group, the total effective rate is 90.00% (72/80), while in control group, the total effective rate is 67.50% (54/80); 6mo after therapy: in combined group, the total effective rate is 88.75% (71/80), while in control group, the total effective rate is 63.75% (51/80); 1y after therapy: in combined group, the total effective rate is 83.75% (67/80), while in control group, the total effective rate is 47.50% (38/80).

By *t*-test, there is no statistically significant difference in the curative effect of two groups before therapy ($P=0.81$). The difference shows statistically significance on different stages of time after therapy ($P<0.05$): the combined group has improved and stabilized the vision more effectively, and reduced edema and bleeding dramatically. The results are shown in Table 1.

Fundus angiography (FFA/ICGA) After 1wk therapy: in combined group, the effective rate on leakage improving is 88.75% (71/80), while in control group, the effective rate on leakage improving is 62.50% (50/80); 1mo after therapy: in combined group, the effective rate on leakage improving is 91.25% (73/80), while in control group, the effective rate on leakage improving is 65.00% (52/80); 6mo after therapy: in combined group, the effective rate on leakage improving is 86.25% (69/80), while in control group, the effective rate on leakage improving is 61.25% (49/80); 1y after therapy: in combined group, the effective rate on leakage improving is 78.75% (63/80), while in control group, the effective rate on leakage improving is 51.25% (41/80).

By *t*-test, there is no statistically significant difference in the curative effect of two groups before therapy ($P=0.79$). The difference between the two groups shows statistically significance in different time periods in terms of improving leakage after therapy ($P<0.05$). The results are shown in Table 2. The leakage stopped and leakage reduced in combined group are better than that of in the control group. The leakage of the eyes is reduced significantly after combined therapy.

Optical coherence tomography (OCT) Before therapy, CMT of the combined group and the control group are (468.72±46.34) μm and (456.59±38.53) μm respectively, there is no statistical significant difference in the two groups ($P=0.74$). After 1wk, 1mo, 6mo and 1y treatment, the CMT are (347.43±36.96) μm and (423.58±29.03) μm, (287.78±34.16) μm and (387.14±32.98) μm, (301.75±37.21) μm and (415.40±31.38) μm, (326.17±27.39) μm and (436.44±35.49) μm respectively, compared between the two groups, and the differences are statistically significant ($P=0.001, 0.005, 0.003, 0.007$). The results have shown

Table 3 The two groups in macular edema absorption of OCT compare different time periods

(CMT/μm)

Group	Before therapy average CMT	After therapy			
		One week	One month	Six months	One year
Combination group	468.72± 46.34	347.43±36.96	287.78±34.16	301.75±37.21	326.17±27.39
Control group	456.59±38.53	423.58±29.03	387.14±32.98	415.40±31.38	436.44±35.49
P	0.74	0.001[a]	0.005[a]	0.005[a]	0.007[a]

[a]Statistically significant ($P<0.05$).

in Table 3. By the end of the therapy, the combined group is more effective on improving the patients' condition, and macular edema is significantly reduced compared with the control group.

Intraocular Pressure Among all the cases in this experiment, no case gets higher intraocular pressure, and intraocular pressure of patients with pre-therapy and post-therapy are within the normal range.

Adverse Reactions There is 1 case occurred in patients suffering from mild pain in the eye 1d after the intravitreal injection of Ranibizumab, and accompanied by blurred vision. After checking, the intraocular pressure is in the normal range, but sight has been dropped 1 line. Psychological comfort and adequate rest should be given in 1d. In the following-up observation period, endophthalmitis, cataract, glaucoma and other complications did not occur.

Relapse In the following-up period, there is 1 patient in the combined group had vision loss in 1mo. There are 2 cases had blurred vision in 6mo, and the leakage occurred after implementing fundus angiography. After intravitreal injection once, sight has improved >2 rows after 1wk.

DISCUSSION

Wet AMD often occurred among people aged over 50 and is different from dry AMD which has a slowly progressive vision loss. Patients with wet AMD have vision loss more rapidly, and vision is often decreased significantly in a short time. Therefore, wet AMD is the main type of causing blindness[14,15]. Principles of dealing with wet AMD is taking the treatment of CNV early and avoiding lesions expanded. The ultimate goal of the treatment for exudative AMD is to close CNV. Therefore any method that can make the CNV eliminate or shrink can be applied by stopping bleeding, oozing and the formation of scar machine can preserve the existing visual function. Current methods of treatment for wet AMD are laser photocoagulation, macular CNV removal, macular translocation surgery, thermotherapy, photodynamic therapy and anti-angiogenesis drug treatment. In this case, patients could have different choices according to their specific circumstances. Due to the poor prognosis of wet AMD, there is no uniform cognition of various treatment methods, hence the treatment of exudative AMD is still one of the problems that researchers from ophthalmology are eager to solve[16,17].

TTT is a promising treatment recently. With the advantages of safe, painless, and low cost, the new method of treatment can be accepted by the majority of patients. The principle of TTT treatment is by using a semiconductor 810 nm wavelength infrared laser on the lesion application which can increase the temperature of the irradiated area by 5-10℃ and promote the macular area renewal intravascular thrombosis and occlusion which will close CNV, so as to achieve the goal of treatment of macular area CNV[18]. Different from the traditional laser photocoagulation, TTT causes so little damage on the nearby tissues due to the moderate temperature. In recent years, anti-VEGF agents become a new anti-angiogenesis targeted therapy, and have achieved good results in terms of the clinical treatment of AMD. At the moment, the only anti-VEGF drugs approved by the US Food and Drug Administration (FDA) approval of anti-VEGF drugs to cure eyes is Ranibizumab which is made of artificial improved rat polyclonal anti-restructuring over the span of derived VEGF antibody. The polyclonal antibody can be combined with all isomer VEGF and become inactivated, so as to inhibit the formation of choroidal neovascularization. Because the polyclonal has a smaller molecular weight, it can better penetrate the retina, increase vitreous body bioavailability up to 50%-60%, and possess good efficacy and safety, and it becomes one of the hot topics in recent years[19].

With the continuous development of medical research, combined therapy has become an emerging treatment, bring to the treatment of patients with dawn, but TTT combined intravitreal Ranibizumab treatment of wet AMD has not been reported. As TTT and intravitreal Ranibizumab have different mechanisms, there are limitations when used alone in the treatment of wet AMD. As we know, when using Ranibizumab alone, the number of intravitreal injection will increase, specifically, the average number is about two or three times or more. So the experiment aims to combine the two treatments of wet AMD, in order to improve the effectiveness of treatment and reduce the adverse reactions. In the final observation period of this experiment, 34 people in combined group whose best corrected visual acuity are improved, and the total effective rate is 83.75% (67/80). In control group, 16 people whose best corrected visual acuity are improved, and the total effective rate is 47.50% (38/80). The difference between the two groups is statistically significant ($P<0.05$), and it shows the combined group yields more effective in improving and stabilizing vision. After 1wk, 1mo, 6mo and 1y therapy, the fluorescent penetrant improves efficiency and CMT in the two groups. The differences in terms of leakage improving and edema reducing are statistically significant ($P<$

0.05), the leakage stop and leakage loss of the combined group are better than that in the control group. After suffering through the eyes of combined therapy, significantly reduced leakage, and combined group is more effective on improving patients' conditions, macular edema is also significantly reduced. Studies have shown that with intravitreal injection of Ranibizumab, postoperative intraocular pressure is a major complication, but there is no case of intraocular pressure happened in this experiment. Intraocular pressure in patients with pre-therapy and post-therapy are within the normal range, there is 1 case occurred in patients suffering from mild pain in the eye 1d after intravitreal injection of Ranibizumab, and accompanied by blurred vision. But with no special treatment, the symptoms ease soon, hence intravitreal injection of Ranibizumab with TTT is safe, reliable, and has less side effects. In the following-up period, only three cases out of the combined group of patients in the treatment need one more intravitreal injection. It shows that intravitreal injection of Ranibizumab with TTT can significantly reduce the number of intravitreal injections, and maintain long-term treatment effect.

In the combined group, we use intravitreal injection of Ranibizumab with TTTamong patients with wet AMD. The results have shown a significant effect in terms of the improvement of visual function, the reduction of injection frequency, the reduction of macular edema, oozing and bleeding, and the prevention of recurrence and other aspects[20,21]. But the mechanism of combined therapy, and the number and interval of Ranibizumab injections still remains to be further investigated.

REFERENCES

1 Pan XM, Wang XR, Liu L, Li HY. Transpupillary thermotherapy in the treatment of retinal arterial macroaneurysms. *Guoji Yanke Zazhi* (*Int Eye Sci*) 2010;10(4):786-787

2 Congdon N, O'Colmain B, Klaver CC, Klein R, Munoz B, Friedman DS, Kempen J, Taylor HR, Mitchell P; Eye Diseases Prevalence Research Group. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol* 2004;122(4):477-485

3 Ngai LY, Stocks N, Sparrow JM, Patel R, Rumley A, Lowe G, Smith GD, Ben-Shlomo Y. The prevalence and analysis of risk factors for age-related macular degeneration: 18-year follow-up data from the Speedwell eye study. United Kingdom. *Eye* (*Lond*) 2011;25(6):784-793

4 Machalińska A, Kawa MP, Marlicz W, Machaliński B. Complement system activation and endothelial dysfunction in patients with age-related macular degeneration (AMD): possible relationship between AMD and atherosclerosis. *Acta Ophthalmol* 2012;90(8):695-703

5 Abedi F, Wickremasinghe S, Richardson AJ, Islam AF, Guymer RH, Baird PN. Genetic influences on the outcome of anti-vascular endothelial growth factor treatment in neovascular age-related macular degeneration. *Ophthalmol* 2013;120(8):1641-1648

6 Kaiser PK, Symons RC, Shah SM, Quinlan EJ, Tabandeh H, Do DV, Reisen G, Lockridge JA, Short B, Guerciolini R, Nguyen QD; Sirna-027 Study Investigators. RNAi-based treatment for neovascular age-related macular degeneration by Sirna-027. *Am J Ophthalmol* 2010;150(1):33-39

7 Martin MA, Reichel E. Tranpupillary thermotherapy for age-related macular degeneration: long-pulse ptotocoagulation, apoptisis, a heat shock proteins. *Ophthalmic Surg Lasers* 2000;31(5):359-373

8 Monika A. Malecha, MD; Barrett G. Haik, MD; William R. Morris, MD. Capillary hemangioma of the optic nerve head and juxtapapillary retina. *Arch Ophthalmol* 2000;118(2):289-291

9 Kaiser PK. Emerging therapies for neovascular age-related macular degeneration: drugs in the pipeline. *Ophthalmology* 2013; 120 (5 Suppl):S11-S15

10 Nguyen DH, Luo J, Zhang K, Zhang M. Current therapeutic approaches in neovascular age-ralated macular degeneration. *Discov Med* 2013;15(8):343-348

11 Synowiec E, Pogorzelska M, Blasiak J, Szaflik J, Szaflik JP. Genetic polymorphism of the iron-regulatory protein-1 and -2 genes in age-related macular degeneration. *Mol Biol Rep* 2012;39 (6): 7077-7087

12 Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR. The estimated prevalence and incidence of late stage age related macular degeneration in the UK. *Br J Ophthalmol* 2012;96(5):752-756

13 Journée-de Korver JG, Oosterhuis JA, Kakebeeke-Kemme HM, de Wolff-Rouendaal D. Transpupillary thermotherapy (TTT) by infrared irradiation of choroidal melanoma. *Doc Ophthalmol* 1992;82(3):185-191

14 Gupta OP, Shienbaum G, Patel AH, Fecarotta C, Kaiser RS, Regillo CD. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. *Ophthalmology* 2010;117(11):2134-2140

15 Hesgaard HB, Torkashvand M, la Cour M. Failure to detect an effect of pneumatic displacement in the management of submacular haemorrhage secondary to age-related macular degeneration: a retrospective case series. *Acta Ophthalmol* 2012;90(6):e498-500

16 Ahfat FG, Zaidi FH. Bevacizumab *vs* ranibizumab-an appraisal of the evidence from CATT and IVAN. *Eye* (*Lond*) 2013;27(3):289-290

17 Dixon JA, Oliver SC, Olson JL, Mandava N. VEGF Trap-Eye for the treatment of neovascular age-related macular degeneration. *Expert Opin Investig Drugs* 2009;18(10):1573-1580

18 Do DV, Schmidt-Erfurth U, Gonzalez VH, Gordon CM, Tolentino M, Berliner AJ, Vitti R, Rückert R, Sandbrink R, Stein D, Yang K, Beckmann K, Heier JS. The DA VINCI study: phase 2 primary results of VEGF Trap-Eye in patients with diabetic macular edema. *Ophthalmology* 2011;11(8):1819-1826

19 CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011;364(20):1897-1908

20 Bressler NM, Bressler SB, Childs AL, Haller JA, Hawkins BS, Lewis H, MacCumber MW, Marsh MJ, Redford M, Sternberg P Jr, Thomas MA, Williams GA; Submacular Surgery Trials (SST) Research Group. Surgery for hemorrhagic choroidal neovascular lesions of age-related macular degeneration: ophthalmic findings: SST report no. 13. *Ophthalmology* 2004;111(3):1993-2006

21 Agarwal M, Chaudhary SP, Narula R, Rajpal S. Pneumatic displacement and intravitreal bevacizumab for management of submacular hemorrhage in choroidal neovascular membrane. *Indian J Ophthalmol* 2010;58(11):170-173